

REMARKS

Upon entering the above amendments, claims 1-6 and 8-24 will be pending in this application and are presented for examination. Claims 1-24 stand rejected. Claim 7 has been canceled without prejudice or disclaimer. Claims 1-6, 8-21 and 24 have been amended.

At the outset, Applicants and their representative wish to thank Examiners Gollamudi and Hartley for the personal interview held on June 30, 2003. During this interview, a number of issues were clarified and an amendment was proposed that have helped the Applicants to more fully address the concerns of the Examiners. Applicants thank Examiners Gollamudi and Hartley for their time and the courtesy of extending the personal interview.

Support for the addition of the phrase "the final product ..." to claims 1 and 21 finds support in the specification at page 4, lines 12-14 and lines 23-27. Support for the amendments regarding organic and mineral acids can be found in original claims 7 and 8 as filed, as well as in the specification at page 2, lines 24-28 and page 3, lines 3-6. Reconsideration of the application is respectfully requested in view of the above amendments to the claims. Applicants believe no new matter is present in this or any other portion of the present amendment.

Applicants have amended the claims to more particularly point out and distinctly claim the subject matter regarded as their invention. Applicants have claimed a preferred embodiment which recites specific acids. The claimed composition permits the inclusion of an increased percentage of an active ingredient, but without the disadvantages associated with a high polyhydric alcohol concentration. This is accomplished in part, with an acid in an amount to substantially completely solubilize the active ingredient. Applicants have surprisingly discovered that by adjusting the acid concentration of the composition the solubility of the active ingredient can be significantly increased without the necessity of utilizing large amounts of polyhydric alcohol.

I. Di Schiena is the Closest Prior Art

The Examiner has maintained the rejection of claims 1-23 of the present invention under 35 U.S.C. § 103(a) in view of Yu *et al.* (U.S. Patent No. 5,571,841) by itself or in

combination with Kasting *et al.* (U.S. Patent No. 5,041,439), or vice-versa. The Examiner has further maintained the rejection of claims 11 and 24 of the present invention under 35 U.S.C. § 103(a) in view of Yu *et al.* by itself or in combination with Kasting *et al.*, or vice-versa, in further view of Uchikawa *et al.* (U.S. Patent No. 5,156,836).

The present invention claims a composition with **at least 5%** of a piperidinopyrimidine derivative in combination with **less than 10%** of an aromatic or polyhydric alcohol. In stark contrast, Yu *et al.*, Kasting *et al.* and Uchikawa *et al.* **all** teach compositions with **less than 5%** of a piperidinopyrimidine derivative in combination with **greater than 10%** of a polyhydric alcohol. Applicants submit that the combination of greater than 5% piperidinopyrimidine derivative in combination with less than 10% polyhydric alcohol is **not** mere optimization, as alleged by the Examiner. Applicants continue to assert the previous remarks set forth in responses dated February 20, 2002 and September 23, 2002, which are hereby incorporated by reference.

Applicants respectfully submit that Di Schiena (U.S. Patent No. 4,866,067), and not Yu *et al.* or Kasting *et al.* or Uchikawa *et al.*, either alone or in combination, is the closest prior art.

Di Schiena teaches topical formulations (lotion, foam, cream and gel) that are useful for the treatment of hair loss or of pathologic forms. In contrast, the present invention claims a **homogeneous** pharmaceutical composition wherein the final product can be a solution, lotion, ointment, mousse, a foam that breaks with shear, spray, aerosol, shampoo, conditioner, gel, cream or paste. In addition, the present invention claims a method for treating hair loss through the topical administration of a **homogeneous** pharmaceutical composition of the present invention.

As the Examiner is aware, MPEP § 716.02(e) sets forth:

The claimed invention may be compared with prior art that is closer than that applied by the Examiner

Applicants may compare the claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner. *In re Holladay*, 584 F.2d 384, 199 USPQ 516 (CCPA 1978); *Ex parte Humber*, 217 USPQ 265 (Bd. App. 1961).

Accordingly, Applicants respectfully submit that Di Schiena is the closest prior art.

II. The Instant Application is Patentable in view of Di Schiena

While Applicants believe that Di Schiena is the closest art to the present application, Di Schiena does not present a bar to patentability of the present application under 35 U.S.C. §§ 102, 103, in view of the amendments to the claims and the surprising results provided in the attached copy of the declaration of Albert Zorko Abram (“the Abram declaration”)¹. Furthermore, Applicants maintain that a *prima facie* case of obviousness has not been established. However, the comparative data filed herewith rebuts any *prima facie* case of obviousness. Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillon*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990).

As will be explained in greater detail below, Applicants prepared Example 3(e) as taught by Di Schiena. Although Di Schiena is silent as to the heterogeneous nature of the Example 3(e) formulation, the attached Abram declaration clearly demonstrates that the formulation of Di Schiena is, in fact, ***heterogeneous***. Di Schiena teaches a ***heterogeneous*** formulation which uses 3-carboxypyridine N-oxide also known as ***oxyniacic acid***. Di Schiena does not teach or suggest a ***homogeneous solution*** and the specific acids presently taught and claimed.

In this regard, the Examiner’s attention is respectfully directed to the enclosed Abram declaration. Mr. Abram declares in paragraph 3 that he is a senior chemist and has been employed doing dermatological product development for the last 15 years (see also Exhibit A of the Abram declaration). As Mr. Abram declares in paragraph 13, he performed a side-by-side comparison of the formulation as disclosed in the subject application (“inventive”) against the Di Schiena formulation (“comparative”) and found unexpected advantages in the inventive formulation not present in the comparative formulation.

¹ The Abram declaration was submitted in U.S. Application No. 10/124,197, pending.

As set forth in paragraph 14, after mixing the constituent parts of the comparative foam formulation (“see Di Schiena example 3(e) foam, col 3, lines 29-38”) the resulting mixture was brown in color (see Exhibit B). The formulation of Di Schiena separated into 2 phases (biphasic) upon standing; the bottom layer was brown and opaque, and the top layer was a dark brown color and clear.

Mr. Abram declares in paragraph 15 that, after mixing the constituent parts of the inventive foam formulation, the resulting mixture was a clear and colorless single-phase solution. The homogeneous nature of the inventive formulation has several advantages, including foam consistency, longer shelf-life, and most importantly, uniformity of dosing. Uniformity of dosing is an important feature of the inventive formulation as it reduces deleterious side-effects known to accompany an administered dose greater than that prescribed. Additionally, as discussed in paragraph 20 of the Abram declaration, the inventive formulation is stable over long periods of time and at elevated temperatures. However, under the same conditions, the formulation of Di Schiena develops an insoluble crystalline precipitate.

As is currently taught and claimed, the foam of the present invention breaks with shear, which significantly eases topical application. Paragraphs 23-28 of the Abram declaration demonstrate, the inventive foam is relatively stiff below 30°C, but is easily broken down under mechanical shear above 30°C. This temperature is significant, since, in preferred embodiments, the foam is applied topically to the human skin, which has a temperature above 30°C. Unlike the inventive foam, the Di Schiena foam exhibits minimal deformation under mechanical shear over the whole temperature range. Even at 40°C, the Di Schiena foam persists while the inventive sample *no longer exists as a foam*. (See Exhibit C of the Abram declaration). As declared in paragraph 29:

Based on the findings of this study, it would be expected that the inventive foam system is rapidly destroyed when applied topically at skin temperature (32°C), whereas the comparative example would be expected to persist as a foam following topical application.

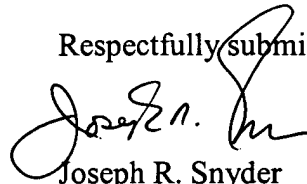
Thus, the present invention show unexpectedly improved solution and mechanical properties. In view of the unexpected and surprising results, as well as the claim amendments, Applicants

submit that Di Schiena does not present a bar under 35 U.S.C. §§ 102, 103, either alone or in combination, to the patentability of the present application.

CONCLUSION

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of all pending claims is earnestly solicited. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

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PATENT
Attorney Docket No.: 021706-000810US

Assistant Commissioner for Patents
Washington, D.C. 20231

On April 1, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: Sylvia E. Arnold

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Tony Wai-Chiu So et al.

Application No.: 10/124,197

Filed: April 16, 2002

For: PHARMACEUTICAL
COMPOSITION

Examiner: Sharmila S. Gollamudi

Art Unit: 1616

DECLARATION UNDER 37 CFR § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Albert Zorko Abram, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.
2. I am currently employed by Connetics Australia Pty Ltd, the assignee of the subject application.
3. I am a Senior Chemist –Technical IP Associate and have been in pharmaceutical research since 1987. I have been employed doing dermatological product development for the last 15 years. My *Curriculum Vitae* is attached herewith. (**Exhibit A**)
4. I have reviewed and analyzed the above-referenced patent application, and I am familiar with the contents therein.

5. I have read the Office Action, dated October 2, 2003, received in the present case, and I have reviewed the references cited therein by the Examiner.
6. It is my understanding that the Examiner has rejected claims 27, 31-36 and 38-46 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 4,866,067 ("Di Schiena") in view of U.S. Patent No. 5,041,439 ("Kasting et al."). For the reasons set forth herein, the Examiner's concerns are overcome.
7. The formulation set forth in column 3, example 3(e) of Di Schiena, entitled "Foam", was recently prepared in our laboratory at Connetics Australia following the teaching of Di Schiena with an understanding of the foam art.
8. The formulation of Di Schiena's Example 3(e) and a formulation of the present invention were prepared.
9. It is my scientific opinion that the Di Schiena formulation was prepared according to the teaching of U.S. Patent No. 4,866,067.
10. Di Schiena teaches the use of a chlorofluorocarbon propellant. However, chlorofluorocarbons ("CFCs") are no longer commercially available in most countries due to their ozone depleting potential and adverse environmental effects.
11. We have therefore substituted an accepted hydrocarbon for the CFCs of Di Schiena at an amount to produce a foam of acceptable quality. We have evaluated the Di Schiena foam over a range of temperatures and are satisfied that the hydrocarbon propellant is a suitable substitute for the CFCs propellant as disclosed in Di Schiena.
12. We performed a side-by-side comparison of the foam as disclosed in the subject application ("inventive") against the Di Schiena foam ("comparative") and found unexpected advantages in the inventive foam not present in the comparative foam.

Advantageous Solution Properties of the Inventive Formulation

13. After mixing the constituent parts of the comparative foam formulation (see Di Schiena example 3 (e) foam, col 3, lines 29-38) the resulting mixture was a brown color (**Exhibit B**). The formulation separated into 2 phases (biphasic) upon standing. The bottom layer was brown and opaque and the top layer was a dark brown color and clear.
14. By comparison, after mixing the constituent parts of the inventive foam formulation, the resulting mixture was a clear and colorless single-phase solution.
15. In the case of the two phase system of Di Schiena, it is necessary to shake the mixture to ensure homogeneity of the contents. Following shaking, the formulation of Di Schiena

returns to a two phase system upon standing. The inventive example does not require such intervention to dispense the formulation, as it exists as a clear and colorless single-phase solution. The top phase in the comparative example is primarily composed of the propellant. Therefore, the inventive example has the propellant dissolved in the system. If the propellant exists as a separate phase this will impact the foam-consistency, decrease shelf-life and most importantly, impart irregularity in dosing.

16. Uniformity of dosing is a major advantage of the inventive foam over the comparative formulation of Di Schiena. A dose of Minoxidil greater than that prescribed can have serious harmful effects to the user. These include, for example, scalp irritation. In the case of systemic absorption, reported side effects include salt and water retention, generalized and local oedema, pericardial effusion, pericarditis, tamponade, tachycardia, increased frequency of angina, or, the potentiation of the orthostatic hypotension produced by guanethidine.
17. In addition, the color of the solution has an impact on the color of the foam. It is also understood that a more intensely colored solution (prior to foam formation) will result in the appearance of the foam deviating from white to an off-white or colored appearance. The comparative foam formulation is brown and opaque, whereas the inventive foam formulation is clear and colorless.
18. It appears from the color difference that the comparative example has produced a different chemical entity that is responsible for the brown coloration. The inventive example has no such brown coloration. I have not undertaken any experimentation to identify the brown component in the comparative formulation.
19. Stability studies have also been conducted using the solvent system and teachings of Di Schiena. Two comparative examples were prepared for each of the following formulations, one containing 3% (w/w) minoxidil, the other containing 5% (w/w) minoxidil. Two samples of the inventive formulation containing 5% (w/w) minoxidil was also prepared. One set of samples were stored at 5°C, and the other set were stored at 50°C. Following one-month, no changes in the comparative or inventive samples were observed at 5°C. However, at 50°C, a crystalline precipitate was observed in the comparative example with 5% minoxidil, while the inventive sample contained no such precipitate. The crystal formation in the comparative solvent system indicates potential instability issues with that foam, and also potential incompatibility of the primary formulation components.

Advantageous Mechanical Properties of the Inventive Foam

20. The mechanical shear properties, including shear, viscosity and cone speed, of the inventive and comparative foams were determined using a rheometer applying constant shear stress to the two foam systems over a temperature range 20°C to 40°C. The use of a rheometer allows the rheological characterization of both Newtonian and non-Newtonian fluids. By controlling the shear stress applied to a sample of fluid, one can determine the fluid's internal

resistance to flow (i.e. viscosity) and also the rate at which the applied shear stress deforms the fluid sample (i.e. shear rate). This information allows distinctions to be made between the flow properties of dissimilar fluids and foam systems.

21. The inventive foam was formulated with 5% minoxidil, and the Di Schiena foam was formulated as demonstrated in Example 3(e). Two samples of each foam were subjected to the experimental conditions.
22. The foam samples were evaluated using a Brookfield R/S-CPS Rheometer. A constant shear stress was applied to the foam samples while the temperature was increased from 20°C to 40°C at a constant rate over a 5-minute span. The instantaneous shear rate, viscosity and temperature of each foam sample was recorded for the duration of the experiment. The elapsed time and the speed of cone rotation were also recorded. The results of these experiments are presented in Table 1 and Exhibit C.
23. **Table 1:** table of experimental data

Temperature Range (°C)	Inventive Foam			Comparative Foam		
	Shear Rate (1/s)	Viscosity (Pas)	Cone Speed (rpm)	Shear Rate (1/s)	Viscosity (Pas)	Cone Speed (rpm)
20-25	0	0	0	0.12-0.16	42-83	0.01-0.02
25-30	0.06-774	0-83	0-109	0.06-0.24	21-83	0.01-0.04
30-35	656-4840	0.001-0.008	10-807	0.12-0.3	17-42	0.02-0.05
35-40	maximum exceeded	maximum exceeded	maximum exceeded	0.18-0.78	6-42	0.02-0.13

24. As the temperature approaches 30°C, the inventive foam appears to soften dramatically. The applied shear stress is able to deform and subsequently destroy the foam structure. The results show a large increase in the rate of deformation (shear rate increases from 0.06/s to 774/s), a rapid change in sample viscosity as the sample is destroyed from zero Pas to 83 Pas and then to 0.008 Pas, as well as an increase in the cone speed (from zero to 109 rpm).

25. Above 30°C, the inventive foam is destroyed. The shear rate and cone rotation speed both increase exponentially until the maximum speed of the instrument is exceeded. The reported viscosity of the system is very low, which is consistent with the destruction of the foam.
26. The comparative example, however, undergoes only a slight change in mechanical properties with the application of a constant shear stress and increasing temperature. The results indicate that the applied shear stress is able to induce deformation of the comparative example immediately and continuously over the entire temperature range studied. The viscosity of the foam was reduced slightly as the temperature increased (from 83 Pas to 6 Pas), while the cone speed remained relatively constant (speed range from 0.01 to 0.13 rpm). The comparative foam structure persists for the duration of the experiment, i.e., the foam is not destroyed.
27. The conclusions of these shear experiments are the following: (1) at 20°C, the inventive foam sample is stiffer than the comparative foam sample; (2) at 30°C, the inventive foam sample is destroyed whereas the comparative foam sample persists; and (3) at 40°C, the comparative foam sample persists whereas the inventive sample no longer exists as a foam.
28. Based on the findings of this study, it would be expected that the inventive foam system is rapidly destroyed when applied topically at skin temperature (32°C), whereas the comparative example would be expected to persist as a foam following topical application.

The declarant has nothing further to say.



Albert Zorko Abram

1 April 2003

Date

Curriculum Vitae

Personal Details

Name Albert Zorko Abram
Address 3 Abbey Court
Wantirna
Victoria
Australia, 3152

Education

Post Secondary Bachelor of Science
Monash University
Completed in 1997
Secondary 1984
High School Certificate
Haileybury College

Work History

Job Details January 2003 - present
Senior Chemist Technical IP Associate
Connetics Australia Pty Ltd

Responsibilities Oversee and provide technical leadership for company R&D programs in line with agreed corporate objectives
Liaise with intellectual property professionals to facilitate the drafting of patent specifications
Coordinate technical activities in line with agreed intellectual property areas
Provide technical advice for intellectual property matters
Provide technical reviews of intellectual property pertinent to key in-house technologies
Keep abreast of new technologies and technical developments
Draft and issue company procedure forms to facilitate the running of the laboratory
Ensure that the company's quality systems are fully operational at all times
Interview prospective employees and train the Formulation Chemists in core scientific activities
Review of monthly technical progress reports
Provide technical service, advice and assistance to company divisions and clients
Provide technical leadership to ensure smooth and effective running of the laboratory
Provide technical advice to company staff and clients as required
To ensure all work in the laboratory is conducted in a safe manner in line with the company's safety policies

Job Details July 2001 – December 2002
Senior Chemistry Supervisor
Soltec Research Pty Ltd/Connetics Australia Pty Ltd
(Company name change to Connetics Australia Pty Ltd in October 2002)

Responsibilities Manage formulation team projects
Prepare formulation development proposals
Prepare project plans in consultation with formulation development teams
Propose new research proposals and conduct research activities to evaluate project feasibility
Keep abreast of new technologies and technical developments
Draft and issue company procedure forms to facilitate the running of the laboratory
Ensure company's quality systems are fully operational at all times
Interview prospective employees and train the Formulation Team's personnel
To approve, allocate and coordinate projects to completion
Submission of monthly technical progress reports
Provide technical service, advice and assistance to company divisions and clients
Ensure smooth and effective running of the Dermatology/Formulation Team
Ensure an orderly and prioritised progression of all development work and provide technical advice to company staff and clients as required
To ensure all work in the laboratory is conducted in a safe manner in line with the company's safety policy
Provide technical advice for intellectual property matters

Key Achievements Contributing author for "Barel/Maibach/Paye :Handbook of Cosmetic Science and Technology"
Primary project liaison for key product development programs

Job Details July 1999 – July 2001
Team Leader, Dermatology
Soltec Research

Responsibilities Manage and coordinate the drafting and issue of MSDS, product specifications, manufacturing methods, product development proposals, reports and procedures.
Maintain the computer database relating to research, development and product evaluation work
Keep abreast of new technologies and technical developments
Draft and issue company procedure forms to facilitate the running of the laboratory
Ensure Soltec's quality systems are fully operational at all times
Interview prospective employees and train the Dermatology Team's personnel
To approve, allocate and coordinate projects to completion
Submission of monthly technical progress reports
Provide technical service, advice and assistance to company divisions and clients
Ensure smooth and effective running of the Dermatology Team
Ensure an orderly and prioritised progression of all development work and provide technical advice to company staff and clients as required
To ensure all work in the laboratory is conducted in a safe manner in line with the company's safety policy
Provide technical advice for intellectual property matters

Key Achievements	Primary project liaison for key product development programs
Reason for Leaving Position	Promotion
<hr/>	
Job Details	July 1988 - June 1999 R & D Scientist Soltec Research
Responsibilities	<p>Maintenance and purchase of laboratory equipment</p> <p>Prepare and coordinate project plans</p> <p>Process development</p> <p>Training staff in the art of formulation chemistry</p> <p>Report on research and development activities to management and clients</p> <p>Research and development of pharmaceutical, cosmetic, food, household, veterinary, automotive, industrial, aerosol and agricultural products</p> <p>Develop manufacturing methods and oversee pilot scale and commercial scale product manufacture</p> <p>Source active drug substances, raw materials and packaging for laboratory scale through to commercial scale product manufacture</p> <p>Conduct stability trials on product prototypes and commercial products for the purposes of determining physical and chemical stability, packaging compatibility and shelf-life</p> <p>Project management of product research and development programs</p> <p>Liaise with manufacturers of aerosol products, solid dosage forms and liquid dosage forms for the purposes of improving manufacturing methods and product quality</p> <p>Preparation of technical reports and product dossiers for Soltec technologies</p> <p>Technical assistance for technology transfer</p> <p>Technical assistance for internal Business Development and Marketing</p> <p>Representing the company attend conferences, technical discussions, trade shows and seminars</p>
Key Achievements	<p>Development of commercially successful intellectual property and patented products</p> <p>Development of novel and improved technologies for the delivery of consumer product formulations</p>
<hr/>	
Job Details	May 1987 - July 1988 Laboratory Assistant Soltec Research Pty Ltd
Responsibilities	<p>Perform routine laboratory tasks</p> <p>Acquire hands-on experience and familiarity with common manufacturing equipment and processes in the cGMP manufacture of pharmaceuticals, cosmetics, agricultural, household and aerosol products.</p>
Reason for Leaving Position	Promotion

Short Courses

December 1997
How to Supervise People
Fred Pryor Seminars

August 2000
Problem Solving & Decision Making
Kepner Tregoe

August 2000
Consultative Relationship Development
Maura Fay

August 2000
Edward de Bono's Six Hats Thinking
Advanced Practical Thinking Training Inc.

September 2000
Edward de Bono's Lateral Thinking
Advanced Practical Thinking Training Inc.

October 2000
Project Management
Kepner Tregoe

November 2000
Microsoft Project 98 Levels 1&2
Pollak Partners

January 2001
Time Management
Australian Institute of Management

May 2002
The New Supervisor
Australian Institute of Management

Current Licenses & Accreditation

Drivers' Licence
Fork Lift Operator Licence

Current Professional Membership & Registrations

Association of Profession Engineers, Scientists and Managers Australia
Australian Society of Cosmetic Chemists
Monash Alumni Association Inc.

Languages

First Language English

Other Languages Slovenian - Fluent
German - Conversational & Written Expression

Personal Strengths & Other Competencies

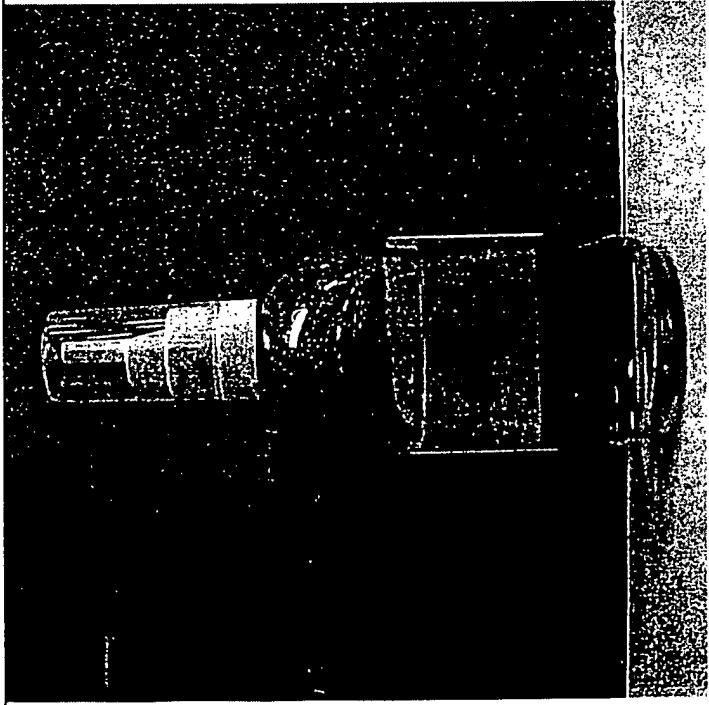
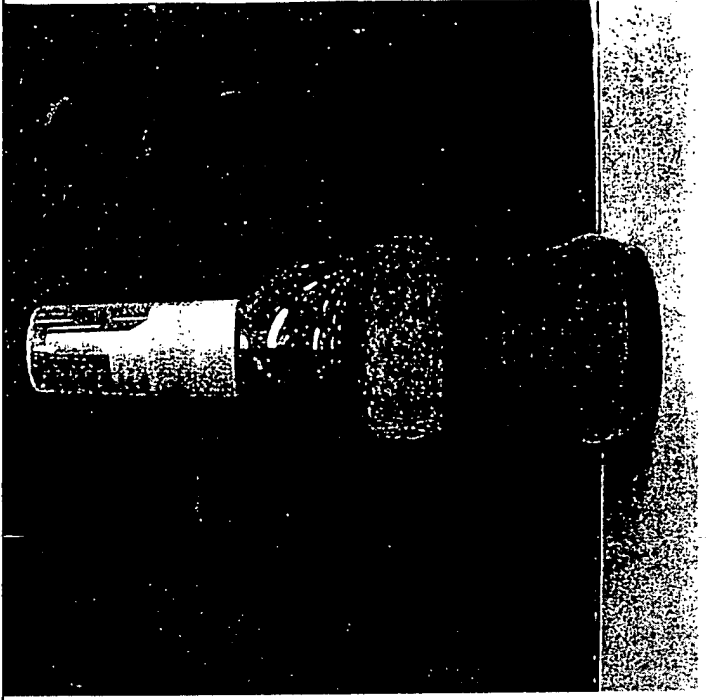
Key Strengths & Skills

Administration - Competent
Budget Preparation - Competent
Computer Literacy - Advanced
Human Resources - Basic
Intellectual Property - Competent
Marketing - Competent
Project Management - Expert
Regulatory Affairs - Competent

Other Key Strengths & Skills

Lateral thinker
Team Player
Commitment to quality, customer service and customer satisfaction
Ability to match theory with reality
Problem solving skills
Interpersonal skills
Chemical industry experience
Pharmaceutical industry experience
Aerosol product experience
OH&S Representative
Member of OH&S Committee
Member of Innovation Management Team
Involvement in cGMP Manufacturing
Involvement in cGMP Clinical Trials
Preparation of Product Development Proposals
Mechanical aptitude
Common sense

Appearance of inventive and comparative aerosol foam examples

Inventive Foam (Connetics Australia)	Comparative Foam (Di Schiena Example 3(e))
	
<p>Description:</p> <p>Clear and colorless single-phase liquid.</p>	<p>Description:</p> <p>Two-phase mixture; comprising a brown, opaque liquid beneath a dark-brown clear liquid.</p>

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Shear rate versus Sample Temperature, E182/71-4, Constant Shear Stress 5 Pa

